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Original Research Manuscript

**EEG Analysis of the Effects of Therapeutic Cooling on
the Cognitive Performance of Multiple Sclerosis Patients**

Leslie D. Montgomery, M.S., Ph.D. *
Richard W. Montgomery, M.S., Ph.D. *
Yu-Tsuan E. Ku, B.Ed., M.S. *
Bernadette Luna, B.S., M.S. #
Hank C. Lee, B.S. *
Mark Kliss, M.S., Ph.D. #

* Lockheed Martin Engineering & Sciences Co	# Mail Stop 239-15
Mail Stop 239-15	NASA Ames Research Center
NASA Ames Research Center	Moffett Field, CA 94035
Moffett Field, CA 94035	

Running Head: Body cooling of MS patients

Correspondence and reprint requests to:

Dr. Leslie D. Montgomery
Mail Stop 230-15
NASA Ames Research Center
Moffett Field, CA 94035

First Author Professional position: Program Manager

TITLE: EEG Analysis of the Effects of Therapeutic Cooling on Multiple Sclerosis Patients' Cognitive Performance

ABSTRACT: The objective of this project was to determine whether a controlled period of head and torso cooling would enhance the cognitive performance of multiple sclerosis patients. Nineteen MS patients (11 men and 8 women) participated in the study. Control data were taken from nineteen healthy volunteers (12 men and 7 women). All but six of nineteen MS patients tested improved their cognitive performance, as measured by their scores on the Rao test battery. A second objective was to gain insight into the neurological effects of cooling. Visual evoked potentials (VEPs) stimulated by a reversing checkerboard pattern were recorded before and after cooling. We found that cooling selectively benefited the cognitive performance of those MS patients whose pre-cooling VEPs were abnormally shaped (which is an indication of visual pathway impairment due to demyelination). Moreover, for female MS patients, the degree of cognitive performance improvement following cooling was correlated with a change in the shape of their VEPs toward a more normal shape following cooling.

Key Words: Multiple Sclerosis, Cooling Therapy, Cognitive Processing, Electroencephalography, EEG

INTRODUCTION:

Neuropsychological studies demonstrate that cognitive impairment is a common symptom of patients with multiple sclerosis^{1,2}. Estimates of cognitive impairment among MS patients range from 43% for a large community-based sample³ to 59% for a large clinic-based sample⁴. In many cases the presence of cognitive impairment affects the patients' daily activities to a greater extent than expected on the basis of their physical disability alone⁵. Cognitive dysfunction can have a significant impact on the quality of life of both the patient and that of their primary care giver. MS-related cognitive dysfunction most often affects short-term memory recall and processing of verbal information⁶.

Namerow⁷ and Syndulko⁸ suggest that MS patients' cognitive processing is degraded by hyperthermia. Therefore, our research focused on the possibility of reversing this relationship. We hypothesized that MS patients would perform cognitive tasks better after therapeutic cooling. We found that this was indeed the case. Thirteen of the 19 MS patients participating in this study had improved scores on the Rao test battery⁹ after a brief period of head and torso cooling. (The Rao test battery is commonly used for quantifying the cognitive performance of MS patients.)

There is also evidence in the literature that MS is associated with conduction blocks in the visual pathway due to demyelination^{2,10,11}. This impairment is associated with abnormally shaped visual evoked potentials (VEPs)^{12,13}. The extent of these abnormalities are routinely used in diagnosing MS^{10,14}. Therefore, we speculated that the beneficial effect of

cooling on cognitive performance might be accompanied by improved visual pathway conduction, which might be shown by a more normal shaped VEP following cooling.

METHODS:

This investigation took place in the research facilities of the Regenerative Life Support Branch at NASA Ames Research Center, Moffett Field, CA and in the facilities of the collaborating MS clinics. Subjects with multiple sclerosis were recruited through the collaborating MS clinics. A total of 12 healthy men and 7 healthy women were tested at Ames Research Center. A total of 11 men and 8 women with MS were tested at the collaborating MS clinics. All subjects gave their written informed consent prior to participation in this research.

All tests were made with the subjects seated in an upright position and conducted at normal room temperature. All tests were conducted for a period of approximately three hours. During this time each subject wore the Life Enhancement Technologies, Inc. (LET, Los Angeles, CA) active liquid cooling garment for a period of one hour. Each test sequence consisted of the protocol described below.

Electroencephalography:

After a training period to familiarize the subject with the test conditions (described below), each subject was instrumented for EEG using the Physiometric, Inc. (Billerica, MA) eNET electrode cap. Nineteen electrode sites were utilized, corresponding to the International 10-20 system¹⁵. Just before cooling, while subjects were seated comfortably in front of a computer screen, continuous multi-channel EEG records were recorded on a Lexicor (Boulder, CO) NRS-24 system (3200x analog gain, 0.5 Hz high-pass filter, 60 Hz notch filter, and maximum scalp Impedance of 5000

ohms). The analog data were digitized at a rate of 256 samples per second.

Stimulus

During the EEG recording period, subjects passively viewed a series of reversing black and white checkerboard grid patterns presented on a computer monitor. The viewing distance and size of the display were controlled to assure that each checkerboard square subtended a visual angle of approximately 18 minutes of arc (as per Harter and White¹⁶). This pattern-reversal stimulus is commonly used for Visual Evoked Potentials (VEPs), which are frequently used for diagnostic evaluation of the extent of visual pathway impairment in MS patients^{10,12}.

VEP Construction

Each pattern reversal, every one-half second, triggered a pulse that was sent to the Lexicor via a pair of Keithly, Inc. (Cleveland, OH) P-I/O-12 cards. These pulses marked the beginning of each stimulus-gated response in the continuous EEG recording. Subsequent to the experiment, the continuous recording was scanned and those stimulus-gated epochs that were free of eye-blink and other artifacts were averaged together to produce a single multi-channel EP for the subject. At least 50 epochs were included in each VEP.

Conversion of VEPs to VEQs

Continuous EEG records and the stimulus-gated VEPs constructed from them are time profiles of voltage differences between scalp electrodes and a reference electrode (linked earlobes in our case). The recorded voltage values are therefore not independent of (unknown) voltage level of the reference. This limitation becomes particularly important when quantitative comparisons are to be made between subjects. Therefore, all

VEPs were mathematically converted to charge-density profiles. The latter, being strictly a function of the derivatives of the contours of the scalp voltage surface, are independent of the unknown voltage level of the common reference ^{17,18}.

The conversion procedure entails two steps: First, at each time sample point in the VEP, the shape of the scalp voltage surface is estimated by multiple regression analysis, using the X-Y grid locations of the electrodes as the independent variables. Then, at each electrode site, the Laplacian of this fitted-surface (the sum of the second-partial spatial derivatives in the X and Y directions) is computed. Charge density is proportional to the (negative of) the Laplacian ¹⁹. The model equation used for the multiple regression estimate of the voltage surface was $V=(a+bX+cY+dXY)^3$, where V is the recorded voltage at a particular electrode site and X and Y are the grid coordinates of the site. Expanded, this is a linear polynomial equation with 16 terms. Prior experimentation has demonstrated that this approach typically produces an estimate with an adjusted R-square value of 0.95 ²⁰. Other researchers have employed spline interpolation methods for this purpose ^{21,22}.

Repeating this procedure at all electrode sites, for all instants in the VEP, produces a set of scalp charge-density time profiles that correspond to the multi-channel voltage profiles of the VEP. For simplicity, we have called this a “VEQ” (the letter Q, commonly used for electrostatic charge, is substituted for the letter P, which stood for potential -- i.e., potential difference, or voltage.)

VEQ data reduction

Calculation of the Laplacian of the scalp voltage data requires multiple electrode data. However, the anatomical projection of the visual pathway suggests that the most relevant VEP (or VEQ) data are obtained from the occipital electrodes. For this reason, we focused the cross subject analysis on the oZ electrode -- actually an artificial electrode, the voltage values for which were obtained as the mean, at each instant, of the adjacent left and right occipital electrodes, o1 and o2.

There is considerable morphological variation in VEPs (and VEQs) for MS patients¹⁴. Therefore, our statistical comparisons focused on the overall “strength” of the VEQ rather than the latency or amplitude of particular waveform features (such as the P100). As an index of the “strength” of the scalp-sensed cortical electrical response to the visual stimulus we employed the absolute value of the time-integral of charge density at oZ during the period from 70 to 200 milliseconds following stimulus presentation.

Neuropsychological assessment tests:

The “Brief, Repeatable Battery of Neuropsychological Tests” referred to as the “Rao test battery”²³ was used to quantify each subject’s cognitive processing before and after cooling therapy. This test battery was developed by members of the Cognitive Function Study Group of the National Multiple Sclerosis Society to serve as a research tool for evaluating short-term changes in cognitive function in patients with MS. The brief, repeatable battery provides measures of sustained attention/concentration (Paced Auditory Serial Addition Test, Symbol Digit Modalities Test), verbal learning and delayed recall (Selective Reminding Test), and visuo-spatial learning and delayed recall (10/36 Spatial Recall Test).

Each subject was given a thorough orientation overview, including practice trials for each individual test, prior to the pre-cooling test sequence. Scores on the individual elements of the Rao battery were combined into pre-cooling and post-cooling 'composite' scores for each subject.

Thermal response measures:

A U.F.I., Inc., (Morro Bay, CA) Biolog battery-powered ambulatory monitoring system was used to record the subject's body temperature, heart rate, and respiration during each seated test sequence. Four U.F.I. 1070 temperature transducers were placed on the subject-- one for chest temperature, one for forearm temperature, one for calf temperature, and one for rectal temperature. A standard Lead I ECG configuration was used to monitor heart rate. Respiration was monitored using an expandable piezoelectric strap placed around the chest. These data were recorded on a Static "Ram Card", then converted and downloaded to a personal computer for analysis. A Thermoscan, Inc. (San Diego, CA) hand-held infrared thermometer was used to take left and right ear canal temperatures. A Becton Dickinson and Company (Franklin Lakes, NJ) digital thermometer was used to measure oral temperature.

Each test period lasted approximately three and one half hours as follows.

- 0 - 30 minutes pre-cooling Rao test
- 30 - 60 minutes instrumentation period
- 60 - 90 minutes control period without cooling
- (Pre-cooling EEG test)
- 90 - 150 minutes cooling period wearing cooling garment
- 150 - 170 minutes recovery period without cooling

(Post-cooling EEG test)

170 - 200 minutes post-cooling Rao test

200 - 210 minutes removal of electrodes and temperature transducers

Subject characteristics

The following inclusion and exclusion criteria were used in selecting subjects for all phases of this investigation. This information was obtained through a screening interview with each candidate subject.

Inclusion criteria for MS subjects

- _ Clinically diagnosed as having MS
- _ Age between 20 and 65
- _ Stable neurologic disability for three months.
- _ Ability to provide informed consent.
- _ Willingness to use a rectal probe for temperature monitoring.

Exclusion criteria for MS subjects:

- _ Neurologic, respiratory, cardiac, endocrine instability.
- _ Excessively overweight.
- _ Evidence of active infection, including urinary tract or pulmonary infections.
- _ Latex sensitivity.
- _ Inability to provide informed consent.
- _ Clinically significant menstrual irregularity in women.
- _ Heat flashes in women due to menopause.
- _ Pregnancy or breastfeeding in women.
- _ Inability of subject to follow standard routine for duration of each test sequence.

- _ Relapse within 30 days.
- _ Significant medical or psychiatric disease.
- _ Inability to fully participate in the study as determined by the attending medical officer.

The mean and standard deviation of the MS and healthy subjects' heights (cm), weights (Kg), and ages (Yr) are given in Table I.

TABLE I HERE

RESULTS:

Thermal response to cooling therapy

FIGURE 1 HERE

Figure 1 illustrates the oral, ear, and rectal thermal responses of the combined male and female MS subject groups as functions of elapsed experimental time (min.). Both the male and female subject groups cooled significantly ($P < 0.05$) during the cooling period. The rectal, ear, and oral temperatures of both subject groups continued to cool during the recovery and post Rao test periods, after the cooling garment was removed. The average skin and average body temperatures of the male and female subjects increased immediately after removal of the cooling garment.

No significant differences were found between the male and female subject groups' thermal changes during any phase of the experiment. The approximate range for

the grouped mean change for each temperature at the time of the second Rao test sequence is: rectal -0.4 to -0.6 °C, oral -0.6 to -0.8 °C, ear -0.3 to -0.4 °C, average skin -1.6 to -1.7 °C, and average body -0.6 to -0.7 °C.

Neuropsychological test response to cooling therapy

All but six of the nineteen MS patients tested (68%) improved their composite cognitive performance scores. Table II shows the number of male and female subjects who improved on each Rao test as a fraction, with the number improved as the numerator and the total number of subjects tested as the denominator.

TABLE II HERE

For those subjects whose performance improved, the average percentage gain in the composite Rao scores was 13.2% for women and 17.5% for men. The largest individual percentage improvement among the women was 30%. Among the men it was 88%.

The results presented above support the hypothesis that therapeutic cooling assists cognitive performance in MS patients. However, there was considerable variance within the sample. Some patients were helped more than others. This variance was not unexpected. Some elements of the Rao test battery, which was used to measure cognitive performance, consisted of problems presented to the patients visually; and yet it is known that a frequent result of MS is degradation of the visual pathway. Therefore, the results of the Rao test were expected to confound pre-post cooling changes in higher-level cognitive performance (e.g., recall and arithmetic) with inter-subject differences in visual pathway degradation.

Electroencephalographic response to cooling therapy

EEG data was collected to provide a degree of experimental control for this confounding factor. As discussed in the Introduction, conduction blocks in the visual pathway due to demyelination frequently result in abnormally shaped VEPs for MS patients. Therefore, it was expected that VEP data would help identify those patients who were at a particular disadvantage for those parts of the Rao battery dependent upon visual acuity.

Usually, VEPs are quantified by measuring the post-stimulus latency or amplitude of characteristic peaks. However, MS patients' VEPs are often so abnormally shaped that the characteristic peaks are hard to identify. Therefore, for the purpose of the experimental control described here, we simply measured the 'strength' of the visual evoked response, defined as the absolute value of the time integral of the waveform during the post stimulus period from 70 to 200 milliseconds. Furthermore, in order to prevent this measure from being influenced by inter-subject differences in the (unknowable) voltage level of the reference electrode, the VEPs were converted in to charge-density waveforms, which we have called VEQs, prior to calculation of the 'strength of response integral.'

FIGURE 2 HERE

Figure 2 shows a typical VEP and the resultant VEQ for the visual stimulus used in this investigation. The light solid line in Figure 2 is the pre-cooling, site o2 grand-average VEP for the 19 healthy control subjects. The familiar features of the VEP are

apparent. The darker solid line shows the corresponding VEQ, calculated for the same scalp location from the Laplacians of the scalp voltage surfaces estimated at each instant in the VEP. The darker curve in Figure 3 will hereafter be referred to as the normal VEQ.

FIGURE 3 HERE

Figure 3 shows the scatterplot of the patients' post-cooling improvement in the Rao composite score versus their pre-cooling VEQ integral. The regression curve fitted to the data implicitly assumes that there is a causal relationship, i.e., that patients' post-cooling improvement on the Rao battery is a function of the strength of their pre-cooling VEQ. The reported R-square value suggests that 77% of the variation in cognitive improvement among the patients can be explained on this basis.

Over most of the range of values for the VEQ integral, the scatterplot also reveals an inverse relationship: Those patients with the strongest VEQs tend to benefit least from cooling. Their Rao scores may even be lower after cooling than before. It appears that those patients who benefit most (in terms of the cognitive functions tested by the Rao battery) are those whose pre-cooling VEQ integrals are between 25% and 75% of normal. Patients whose VEQ integrals were either above or below this range had a decrease in their post-cooling Rao test scores.

This inverse relationship can be used to define three levels of MS patient's VEQ response to a reversing checkerboard stimulus that may be used to predict those patients that may show improved cognition after body cooling.

FIGURE 4 HERE

Level 1 - are those patients with VEQ integrals less than 25% will not be improved by cooling therapy. Their VEQ is abnormal, but does not change due to cooling. Figure 4A (Subject pm10 in Figure 3) is typical of this group. This subject's VEQ is nearly flat over the first 200 msec. during both the pre and post-cooling EEG tests. The Level 1 subjects may be so impaired or have so much nerve damage that cooling does not effect their visual pathway conduction.

Level 2 - (Figure 4B, Subject pm3 in Figure 3) This subject is typical of those patients with VEQ integrals between 25 and 75% of normal. This patient's data point is located near the top segment of the curve that slopes downward to the right (the inverse relationship). His VEQ is somewhat abnormal during both the pre and post-cooling EEG tests. However, his VEQ becomes more "normal" after body cooling. Level 2 patients may have moderately impaired neural conduction due to nerve damage. Cooling may facilitate the performance of their neural conduction and thereby improve their post-cooling cognitive processing.

Level 3 - (Figure 4C, Subject pf8 in Figure 3) This subject is typical of those patients with VEQ integrals greater than 75% of normal. Figure 4C shows that this subject's VEQ was much stronger than that of the healthy control subjects. Therefore, one might conjecture that this subject's visual pathway is healthy. In that case, if the effect of cooling is to improve visual pathway conduction where it is intact but damaged, one would not expect much improvement in this subject's Rao score after cooling. It is not clear why these "Level 3" subjects exhibit a lower Rao score after cooling.

We recognize that the polynomial curve which crosses the horizontal axis at these points, is merely an empirical fit. Nonetheless, this non-linear and generally inverse relationship appears to warrant further study. If it can be assumed that a stronger pre-cooling VEQ indicates less demyelination in the visual pathway, the inverse relationship may be a manifestation of differences in how cooling affects the impulse transmission properties of normal and demyelinated nerve fibers.

Other researchers have already discussed the possibility that cooling may have opposing effects on neural conduction, and that the balance may depend upon the state of demyelination. Schauf and Davis²⁴ developed a theoretical model of a nerve to examine the combined effects of temperature and loss of myelin on conduction.

They show that decreased temperature can have two different effects upon conduction in the nerve fiber. In general, a decrease in nerve temperature will reduce the conduction velocity in normal nerves or in nerves with a small amount of demyelination. In nerves with moderate demyelination a small reduction in temperature may actually increase conduction velocity or reverse the effect of blockage and restore conduction. The model predicts that a temperature decrease of 15 to 20 °C is required to restore conduction in the heavily demyelinated nerve fiber.

They calculated conduction velocity as a function of temperature for a normal nerve fiber and a series of demyelinated nerves ranging from 0.06 to 0.50 times the normal myelin resistance. Conduction velocity was found to increase linearly with temperature in the normal nerve, reaching a broad maximum at approximately 42 °C. A further increase in temperature caused the conduction velocity to drop sharply and completely fail at 50 °C. In demyelinated fibers the conduction velocity also increases

with elevated temperatures, however the slope of the curve is reduced with increased nerve damage and becomes almost horizontal with extensive demyelination. In addition, nerve blockage occurs at lower temperatures with increased demyelination. Blockage takes place at approximately 50 °C in the normal nerve fiber, at approximately 46 °C in the fiber with 50% of the normal resistance, and at ~ 40 °C in the fiber with 33% of the normal resistance. Blockage occurs at temperatures lower than 38 °C when the resistance of the myelin sheath falls below 20% of normal. The model predicts that complete conduction blockage will occur at 28 °C when the myelin resistance is 10% of normal and at 16 °C when the myelin resistance is 6% of normal.

Honan et. al.²⁵ suggest that these results can be used to explain the seemingly paradoxical effect of temperature upon the increased symptoms of some multiple sclerosis patients with slight elevations of temperature and in others with small decreases in body temperature. Elevation of temperature in the unblocked nerve may increase conduction velocity thereby reducing symptoms of MS or it may cause blockage and greatly increase the symptoms. On the other hand a reduction of temperature in the unblocked nerve will reduce conduction velocity and increase MS symptoms or it may restore conduction in a blocked nerve and greatly reduce the symptoms of MS. In nerve tracks which contain individual fibers with different amounts of demyelination changes of temperature can cause a wide range of effects, which, for the most part, will depend upon the summation of the above effects.

In this way, cooling therapy may produce a range of responses when applied to a random population of MS patients. The nature of their impairment and extent of their heat sensitivity should be taken into consideration when use of cooling therapy is

anticipated.

SUMMARY:

Based on these data, we feel it is fair to conclude that the effect of cooling on cognitive performance probably involves a change in visual pathway conduction -- but that this can be statistically confirmed only for the women. There may be gender differences in how the body responds to cooling. Perhaps the effects of cooling were muted for the men.

This study also shows that EEG analysis reveals useful insight into the effects of cooling therapy on MS patients' cognitive performance. EEG data may be used for screening purposes, to identify those patients most likely to experience improved cognitive performance as a result of therapeutic cooling. EEG data is already often collected for clinical diagnostic purposes. To use such data for predictive screening it would be necessary, however, to utilize a multiple electrode grid and to transform the VEPs to charge density VEQs.

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Table I

Subject Characteristics

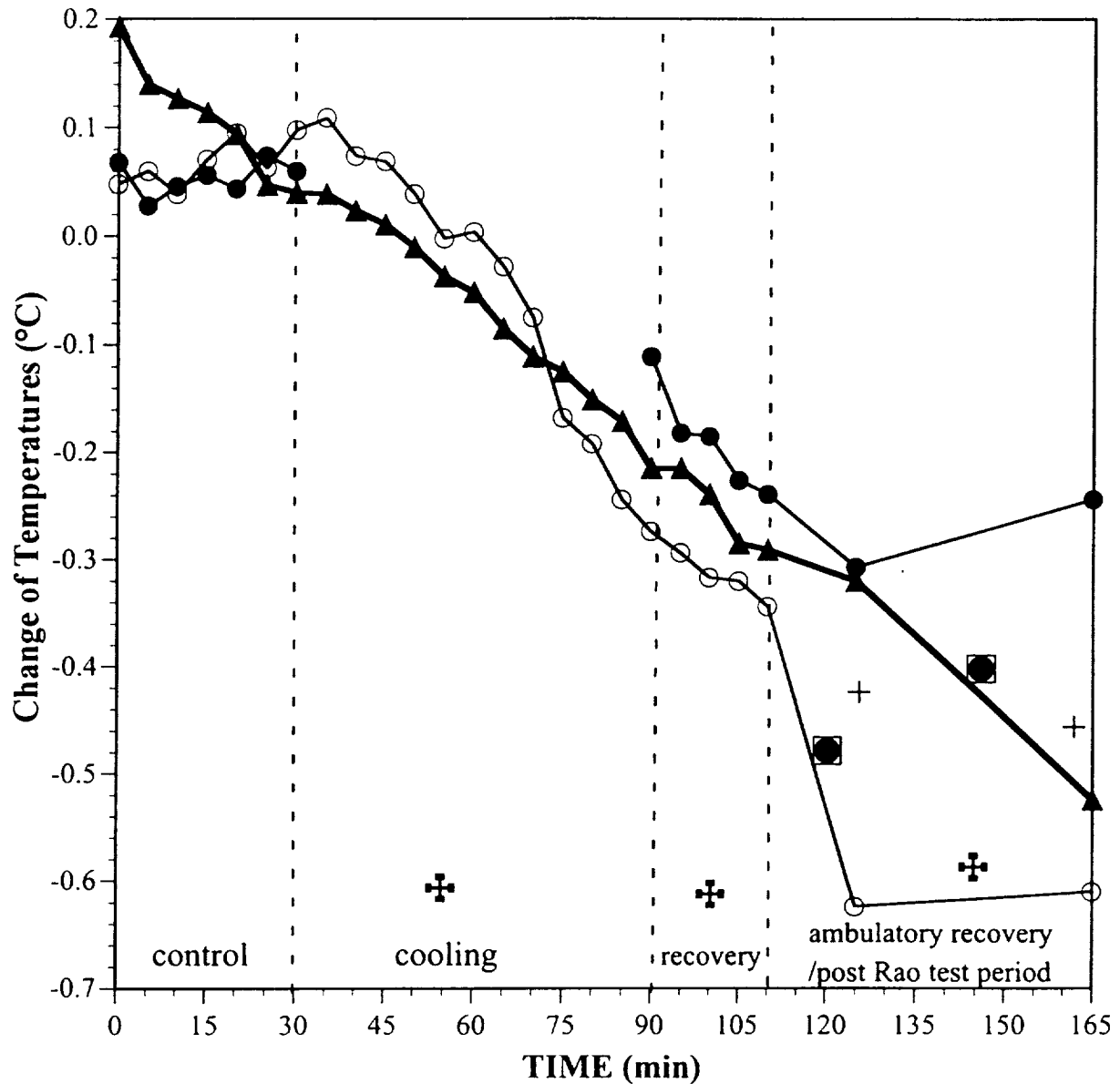
Subject Group	Height	Weight	Age
MS Female	163.0 ± 5.8	77.4 ± 13.8	52.0 ± 7.0
MS Male	177.8 ± 5.1	75.9 ± 7.0	47.7 ± 7.4
Healthy Female	165.7 ± 7.0	67.4 ± 10.5	42.9 ± 9.7
Healthy Male	180.6 ± 5.0	89.8 ± 10.9	43.0 ± 13.7

Table II

Fraction of Subjects Who Improved After Cooling

Test	Males	Females
Selective Reminding	8/11	5/8
10/36 Spatial Recall	4/11	3/8
Symbol Digit Modalities	2/11	6/8
Paced Auditory Addition		
Three Second Interval	6/11	6/8
Two Second Interval	4/11	5/8

Figure 1 Change in oral, ear, and rectal temperature of MS patients in response to body cooling

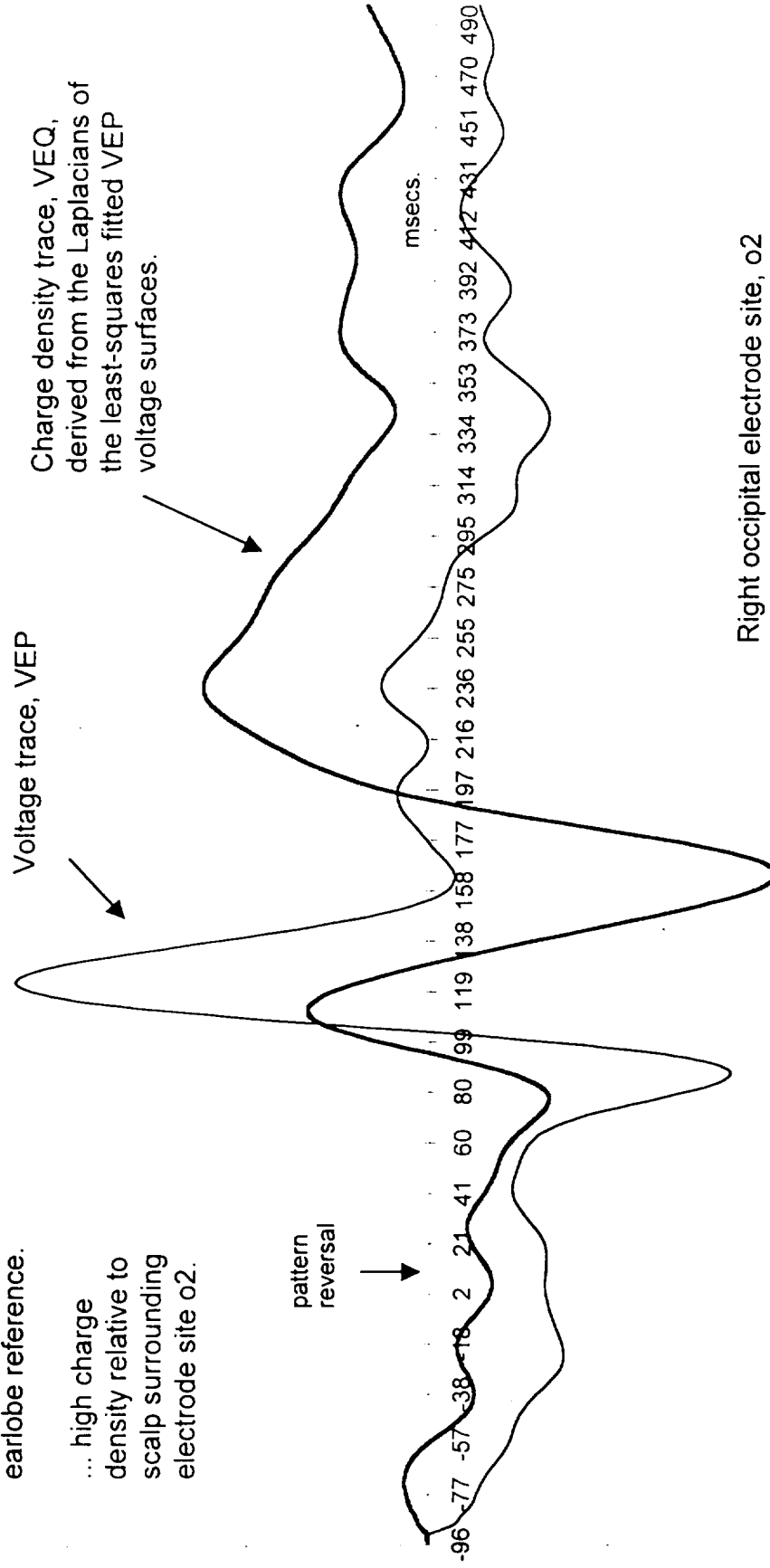


- ✚ significant difference ($P < 0.05$) from mean of control
- significant difference ($P < 0.05$) between the two points (110 and 125, 125 and 165)
- ✚ significant difference ($P < 0.05$) between oral and earl

Upward values =

... positive voltage
relative to linked
earlobe reference.

... high charge
density relative to
scalp surrounding
electrode site o2.



Right occipital electrode site, o2
Reversing checkerboard VEP.
Grand average for 19 healthy adults.

Figure 2. Comparison of a typical VEP with its corresponding VEQ

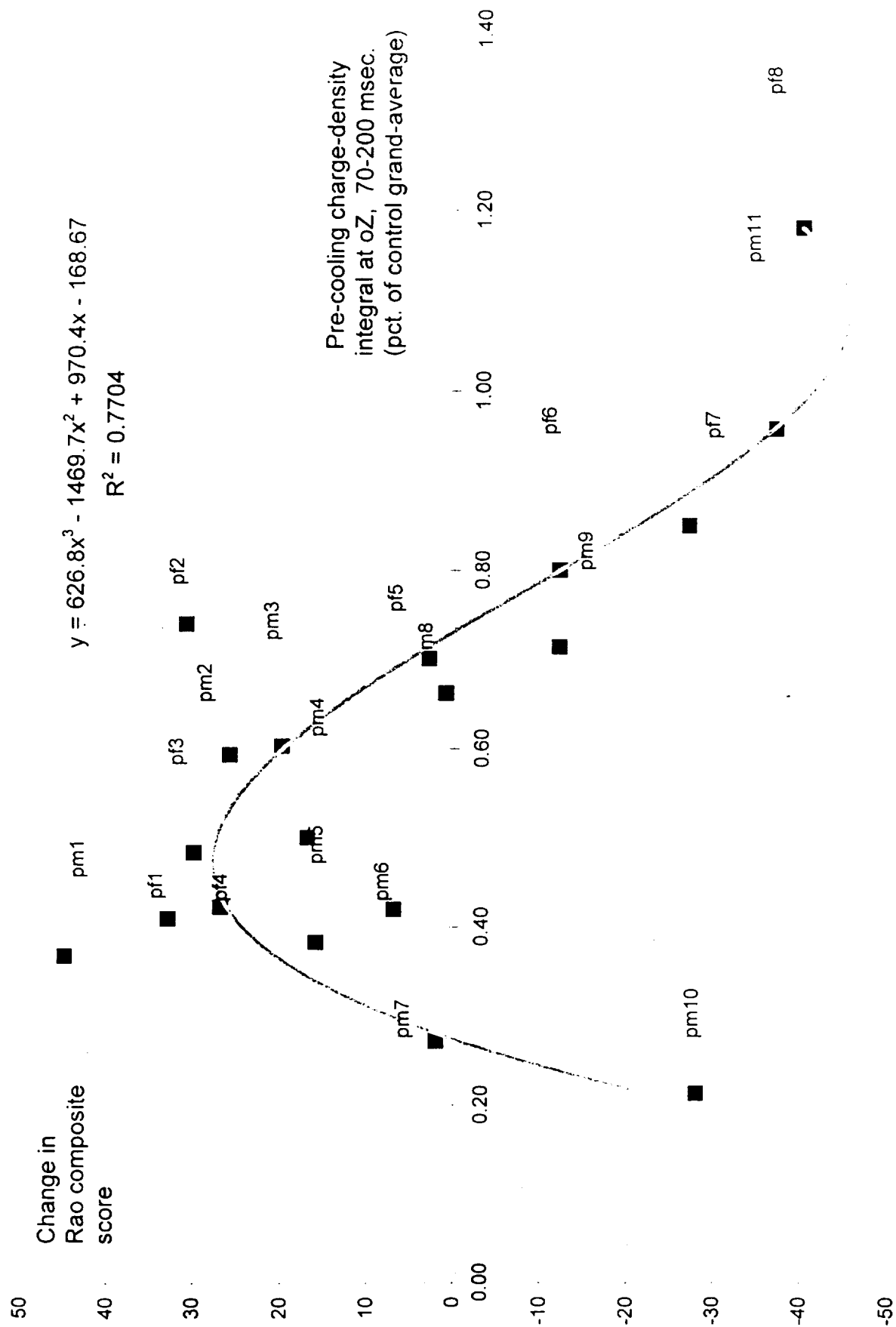


Figure 3. MS patients: Post cooling Rao score change vs. integral of pre-cooling VEQ

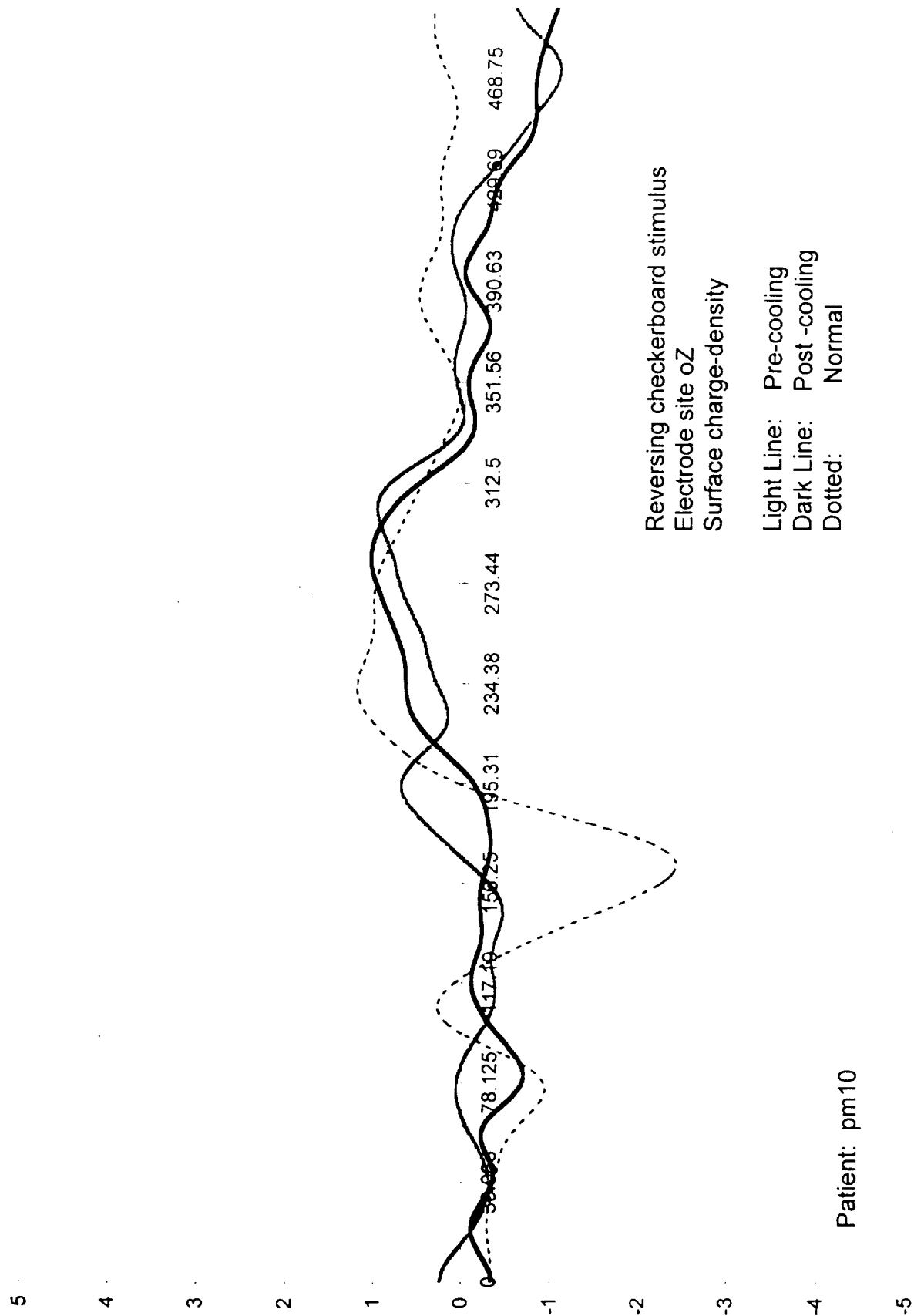


Figure 4A. Typical Level 1 VEQ response before and after cooling

5

4

3

2

1

0

-1

-2

-3

-4

-5

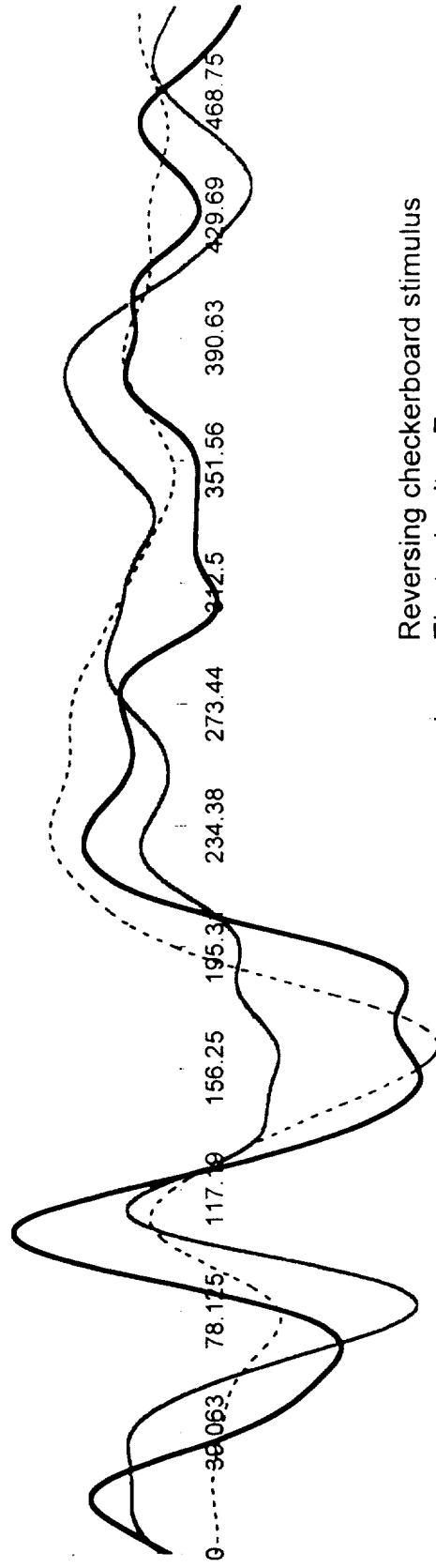


Figure 4B. Typical Level 2 VEQ response before and after cooling

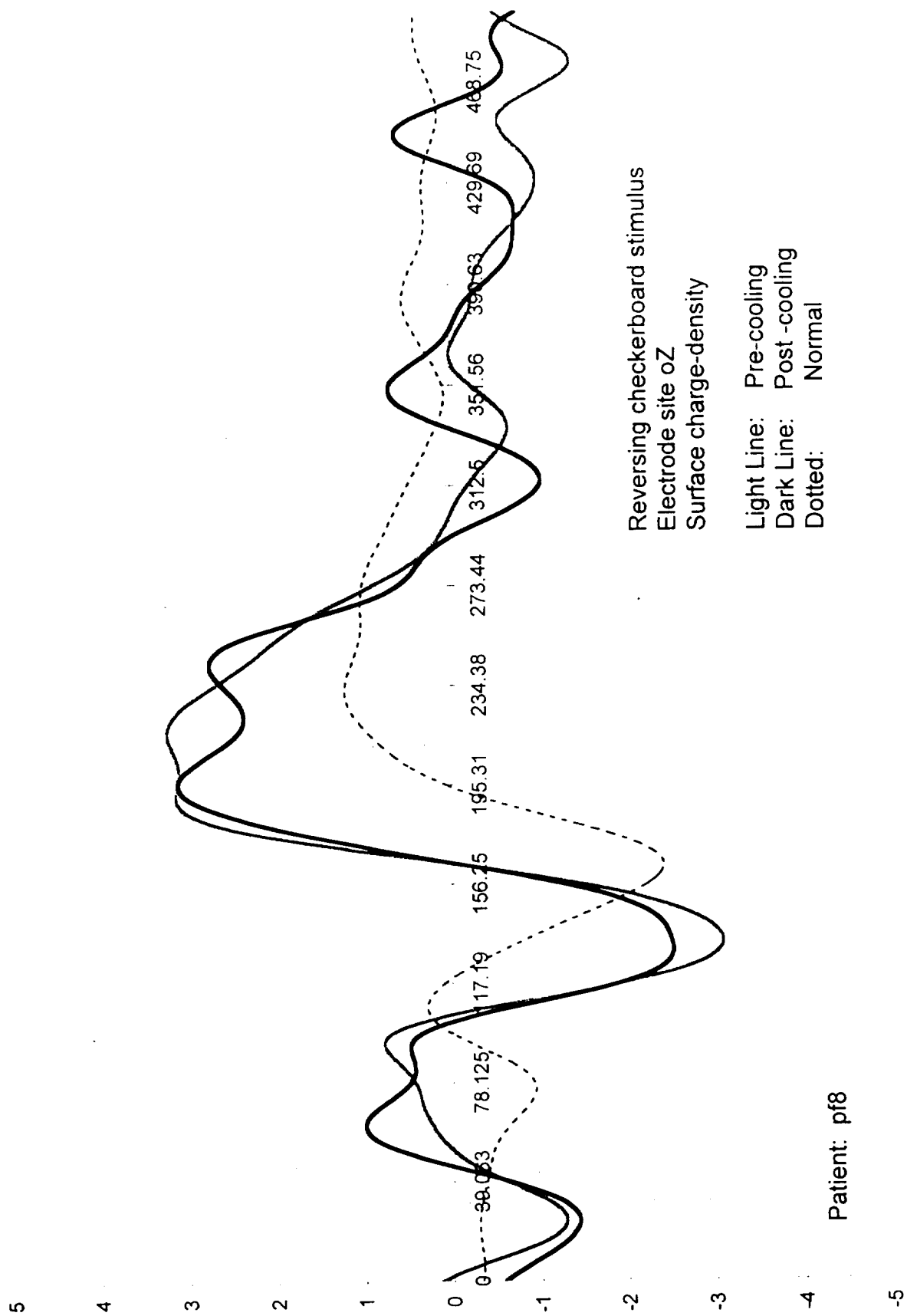


Figure 4C. Typical Level 3 VEQ response before and after cooling

